Journal of the American College of Cardiology Vol. 61, No. 7, 2013

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.11.035

EDITORIAL COMMENT

Ischemia Dictates Outcome, Not Symptoms*

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There has been enormous interest in determining whether the presence or absence of symptoms of myocardial ischemia influence prognosis in patients with coronary artery disease (CAD). The concern has been predicated on the concept that the anginal pain associated with ischemia serves as a safety warning signal indicating the presence of myocardial ischemia and that the absence of a warning signal may enable the patient to continue exercise or emotional stress despite ischemia, exacerbate the dangerous imbalance of myocardial oxygen supply and demand, and potentially cause an ischemia-associated arrhythmia or acute coronary syndrome. These concerns have been further fueled by the appreciation that the vast majority of ischemic episodes in coronary patients are indeed asymptomatic. The prognostic significance of painless ischemia is particularly germane in the management of patients with diabetes because they are at increased risk for the presence of painless myocardial ischemia (1).

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The mechanisms responsible for why some episodes of ischemia are asymptomatic and why some coronary patients' ischemia is consistently asymptomatic have remained unclear. Possible mechanisms have included asymptomatic ischemia being less severe than symptomatic ischemia (2), presence of endogenous opiates that may blunt the perception of cardiac ischemia (3), and abnormal brain processing of afferent pain messages from the heart (4). Autonomic nerve dysfunction may also be responsible for the lack of perception of ischemic symptoms (5), particularly among patients with diabetes, and such autonomic neuropathy is indeed associated with increased mortality and morbidity (6).

The prognostic significance of asymptomatic ischemia, and consequently the most optimal management strategy for such patients, has been an important clinical question since the first appreciation that myocardial ischemia was frequently asymptomatic. The Coronary Artery Surgery Study Registry of patients enrolled from 1974 to 1979 was the first major study indicating that the 7-year survival was dependent not on the presence of anginal symptoms accompanying exercise-induced ischemia but on the severity and extent of coronary obstructions (7). Ischemia identified during ambulatory electrocardiographic (ECG) monitoring of patients with CAD, which is almost always asymptomatic (even in typically symptomatic patients), also identifies patients at increased risk of adverse cardiac events. The ACIP (Asymptomatic Cardiac Ischemia Pilot) study suggested, in a relatively small number of patients, that the 2-year incidence of death and myocardial infarction (MI) was significantly lower among patients randomized to an early revascularization strategy (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]) compared with patients randomized to an early pharmacological strategy, whether based on control of angina or control of ischemia (8).

In this issue of the *Journal*, Dagenais et al. (9) provide important new data concerning the prognostic significance of the presence of anginal symptoms on outcomes over a 5-year follow-up in the BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) study during the enrollment period from 2001 to 2005. They performed a post hoc analysis of 2,364 patients with type 2 diabetes and documented CAD: 1,434 patients with typical angina symptoms; 506 with anginal equivalent of dyspnea, fatigue, or diaphoresis on exertion; and 424 patients with truly asymptomatic ischemia. All patients received optimal medical therapy consisting of lifestyle management targeting smoking cessation, diet, weight loss, and regular physical exercise, and pharmacological therapy to maintain glycosylated hemoglobin <7%, low-density lipoprotein <100 mg/dl, and blood pressure ≤130/80 mm Hg. Patients were randomly assigned to a treatment strategy of prompt coronary revascularization with optimal medical therapy or optimal medical therapy alone and assigned to undergo either insulin sensitization therapy or insulin provision therapy. Dagenais et al. (9) performed 2 analyses to determine the role of symptom status in outcome and response to assigned strategy: all study patients analyzed together, using statistical adjustments to account for effects of confounders including the assigned management strategy, and outcomes analyzed separately within each management treatment strategy on the basis of symptom status. They observed in each analysis that there was no difference in the composite of all-cause death, nonfatal MI, or nonfatal stroke among the 3 groups based on the anginal symptoms at baseline, even though the asymptomatic ischemia group had the greatest magnitude of myocardium at risk compared with the other

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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patients. The investigators acknowledge that because this study was a post hoc analysis, it serves primarily to generate new hypotheses; however, they nevertheless conclude that asymptomatic patients with type 2 diabetes, stable CAD, and documented ischemia were at as high risk as similar patients with anginal symptoms and that all of these patients should be managed similarly in terms of risk stratification and preventive therapies.

How do we incorporate these important findings into clinical care? Should we now aggressively screen all patients with diabetes to determine if CAD and ischemia are present, even those without any symptoms to suggest ischemia, because prognosis is related to ischemic risk and not to anginal symptoms? The prospective studies available to date have not been conclusive in regard to the value of widespread screening of all patients with diabetes to identify those with CAD because the studies have been small, there has been a low prevalence of high-risk CAD in the patients investigated, and the study designs have not included rigorous diagnostic and management strategies (10). Furthermore, the best management strategy once CAD is identified in the patient with diabetes remains somewhat unclear in that the main BARI 2D trial indicated no survival advantage for revascularization as opposed to medical therapy (11). If revascularization therapy is the preferred strategy in high-risk patients with diabetes and multivessel CAD, the recently reported FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) trial indicated that CABG surgery reduced the rate of the primary endpoint of death, nonfatal MI, or nonfatal stroke compared with PCI (12). Given the rapidly escalating epidemic of type 2 diabetes, the costs of widespread CAD screening of low-risk asymptomatic patients with diabetes would likely outweigh the minor clinical benefit (10).

For now, we should certainly optimize risk factor management for all patients with diabetes, and we will need more prospective cost-effectiveness studies to determine an optimal risk stratification strategy for patients with diabetes at risk for CAD. Stepwise risk stratification will likely be the appropriate way to evaluate CAD risk, with careful assessment of risk factors and diagnostic modalities such as stress ECG testing, myocardial perfusion imaging, and calcium scoring (10). Given the epidemic of diabetes that is upon us, as well as the exorbitant health care expenditures that we currently make, we will need to be diligent in carefully assessing the risk, benefit, and cost of widespread screening. If a high-risk patient is objectively identified, even in the absence of symptoms, it will certainly be appropriate to proceed to more detailed high-risk assessment, with consideration of medical versus revascularization therapy. Although the study by Dagenais et al. (9) was a post hoc analysis, it is consistent with prior studies over the past 30 years: prognosis in stable CAD is driven by objective ischemia, not by the nature or magnitude of anginal symptoms.

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Key Words: angina ■ coronary artery disease ■ silent ischemia ■ type 2 diabetes.